

Remarks

Claims 3, 24, 125, 130 and 132 are cancelled without prejudice or disclaimer.

Claims 1, 126-128 and 131 are amended. Support for amendment to claim 1 can be found on page 29 line 24. *In re Johnson*, 558 F.2d 1008, 194 USPQ 187 (CCPA 1977). (A specification that supports a claimed genus also supports that genus minus an explicitly recited species.) A copy of *In re Johnson* is provided herewith for the Examiner's perusal as Exhibit A. Further claim amendments find support as follows: page 9 lines 12-14 and the Examples (claim 1); page 5 lines 13-20, page 6 lines 1-2, page 8 lines 5-6, page 9, lines 12-14 (claim 126); page 5 lines 13-21 (claims 127-128); and previously pending claim 125 (claim 131).

Applicant reserves the right to pursue the subject matter of the originally filed claims in continuing applications.

New claims 133-136 are added. Support for these claims can be found as follows: page 5 lines 13-20; page 8 lines 5-6 (claims 133-134); page 28 lines 1-6 (claim 135); and originally filed claim 8 (claim 136).

No new matter has been added.

Claims 1, 4-9, 11-13, 15-23, 25-28, 126-129, 131 and 133-136 are pending.

Rejection under 35 U.S.C. §112

Applicant acknowledges withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Rejections under 35 U.S.C. §102

U.S. Patent No. 6,727,230 B1 (Hutcherson)

Claims 131 and 132 are rejected under 35 U.S.C. §102(e) as being anticipated by Hutcherson. According to the Examiner, "Hutcherson teaches a method of stimulating a local immune response in selected cells or tissues of an infectious subject or tumor bearing subject ... (by) ... inhaling or administering intranasally ... a synthetic or ISIS oligo containing an unmethylated CpG motif". The Examiner further asserts that "Hutcherson does not teach explicitly that ... a mucosal immune response has been generated as the result of an administration of an ISIS oligo to the mucosal surface, such must necessarily follow as the result of the administration". Applicants respectfully traverse in part.

Claim 131 (and claims dependent thereon) at a minimum requires that a CpG oligonucleotide be administered to a subject. Hutcherson does not anticipate these claims because it does not teach all of the claim limitations either inherently or explicitly. Hutcherson describes methods of stimulating an immune response employing immunopotentiating oligonucleotide analogs having at least one phosphorothioate internucleotide bond, independent of sequence. Hutcherson does not recognize or specifically describe a class of immunostimulatory oligonucleotides having an unmethylated CpG dinucleotide. For Hutcherson to inherently disclose claim 131, one of ordinary skill in the art would *necessarily* have to use a CpG containing oligonucleotide *each and every time* the method of Hutcherson was practiced. There is no support for this position, since the immunostimulatory element of Hutcherson's oligonucleotides is the phosphorothioate internucleotide bond and not any particular sequence motif.

Additionally, Hutcherson does not teach administration of an immunopotentiating oligonucleotide at one mucosal site and exposure to antigen at a different mucosal site. Indeed, the Examiner acknowledges this when he states on pages 2-3 (abridging paragraph) that "ophthalmical, vaginal or rectal administration is also disclosed depending on a target tissue or cells targeted for an administration".

Accordingly, withdrawal of this rejection is respectfully requested.

U.S. Patent No. 6,426,334 B1 (Agrawal)

Claims 131 and 132 are rejected under 35 U.S.C. §102(e) as being anticipated by Agrawal. According to the Examiner, "Agrawal teaches a method of stimulating an immune response and/or cytokines production ... (by) administering intranasally ... a synthetic oligo containing an unmethylated CpG motif". The Examiner further asserts that "Agrawal does not teach explicitly that ... a mucosal immune response (is) generated as the result of an administration of a CpG motif containing oligo to the mucosal surface (but that) such must necessarily follow as the result of the administration". Applicants respectfully traverse in part.

Claim 131 has been amended and new claims 133 and 134 have been added. Agrawal does not anticipate these claims because it does not teach all of the claim limitations either inherently or explicitly. At a minimum, Agrawal does not teach administration of CpG oligonucleotide at one mucosal site and exposure to antigen at a different mucosal site. In order

to inherently anticipate the claim, each and every time one of ordinary skill practiced the method of Agrawal, a CpG oligonucleotide would have to be administered to one mucosal surface and a different mucosal surface would have to be exposed to an antigen. There is no evidence that this is the case.

Accordingly, withdrawal of this rejection is respectfully requested.

U.S. Patent No. 6,218,371 (Krieg '371)

Claims 1, 11, 21, 23 and 24 are rejected under 35 U.S.C. §102(e) as being anticipated by Krieg '371. At the outset, Applicant wishes to point out that the Examiner appears to have misconstrued the scope of the rejected claims. The Examiner has rejected claimed embodiments "drawn specifically to a *combined* use of a CpG motif containing oligo and a cytokine in a subject exposed to an antigen such as subject at risk of having an allergic reaction, or asthmatic subjects" (emphasis added). None of the rejected claims recite all of the afore-mentioned limitations and the Examiner is asked to clarify this statement.

Applicant has previously submitted a Declaration from inventor Heather L. Davis demonstrating that the instant inventors knew prior to the effective filing date of Krieg '371 (i.e., April 3, 1998) and at least as early as November 1997 that mucosal administration of a CpG oligonucleotide could induce a mucosal immune response to an antigen upon antigen exposure. Additionally, it was known prior to the effective date of Krieg '371 that antigens included allergens and that allergens could be used in the treatment (including prevention) of allergies or asthma. Indeed the Examiner acknowledges as much on page 7 of the present Office Action where he states "*at the time the invention was made, the concept of employing a classical antigen and a CpG containing oligo for an induction of an immune response in a subject in need thereof, such as subjects at risk of having an allergic reaction, cancer, or asthma, is well-known in the prior art*" (emphasis added). Accordingly, Krieg is removed as a prior art reference at least for claims 1, 11, 21 and 23.

Applicant further points out that claim 24 recites a method that "further comprises" administration of a cytokine and thus recites a step in addition to the basic limitations of claim 1. Claim 1 should therefore stand or fall independently of claim 24. Without conceding to the Examiner's position with regards to the Davis Declaration but in the interest of expediting prosecution, claim 24 is cancelled.

Accordingly, withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. §103

Hutcherson or Agrawal in view of WO96/02555 (Krieg '555) or US 6,239,116 (Krieg '116)

Claims 1, 3-7, 11-13, 15-23, 26-28 and 125-132 are rejected under 35 U.S.C. §103(a) as being unpatentable over Hutcherson or Agrawal in view of Krieg '555 or Krieg '116. According to the Examiner, "it would have been obvious for one of ordinary skill in the art to employ an ISIS oligo of Hutcherson or a CpG motif containing oligos taught in Agrawal or Krieg(s) in combination with a classical antigen for use in a method of inducing an immune response, wherein an intranasal administration route or any traditional route of administration ... is employed".

Claim 1 has been amended to recite that the oligonucleotide and antigen are administered to the same mucosal site. Claim 131 has been amended as discussed above. Applicant traverses in part.

The combination of references does not result in all of the limitations of claim 1 and claim 131. Hutcherson and Agrawal are discussed above. At a minimum, these references do not teach administration of oligonucleotide and antigen to the same mucosal site (claim 1) or administration of an oligonucleotide to a mucosal site different from the mucosal site that is exposed to an antigen (claim 131). Neither of the secondary references adds to these teachings. Accordingly, the combination of references does not result in each and every limitation of claim 1 (and thus claims dependent thereon) and claim 131 (and claims dependent thereon).

Accordingly, withdrawal of this rejection is respectfully requested.

Hutcherson or Agrawal in view of Krieg '555 or Krieg '116, and further in view of Krieg et al. Trends in Microbiology, 6(1):23-27, 1998 (Krieg 1998)

Claims 1, 8 and 9 are rejected under 35 U.S.C. §103(a) as being unpatentable over Hutcherson or Agrawal in view of Krieg '555 or Krieg '116 and Krieg 1998. According to the Examiner, Krieg 1998 teaches "that alum is effective as a Th2 response inducing adjuvant". The Examiner further states that "it would have been obvious for one of ordinary skill in the art to have employed alum in the immunization methods of the combined cited references". At the outset, Applicant wishes to point out the Examiner's apparent confusion between the nature of an

immune response (e.g., a Th1 or a Th2 immune response) and whether it is a systemic or mucosal immune response. As explained in previous responses, the Th1 or Th2 nature of an immune response says nothing of the systemic or mucosal nature of an immune response. Thus, a mucosal immune response is *not the same* as a Th2 immune response.

There is no motivation to combine the references. For example, Krieg 1998 teaches that “the Th1-like cytokine profile induced by CpG DNA suggests that it will offer significant advantages over alum as an adjuvant”. The reference further characterizes alum as an adjuvant that “induces a Th2- rather than a Th1- immune response and may interfere with CTLs”. This teaches away from the *combined* use of CpG oligonucleotides *and* a non-oligonucleotide mucosal adjuvant such as alum. At most, the reference suggests using CpG oligonucleotides *instead of* alum. Regardless, even if such a combination was made, the addition of Krieg 1998 does not provide the deficiencies of the previous combination of references. In particular, Krieg 1998 does not teach that oligonucleotide and antigen are administered to the same mucosal site (claim 1), nor does it teach administration of oligonucleotide to a mucosal site different from a mucosal site that is exposed to antigen (claim 131).

Accordingly, withdrawal of this rejection is respectfully requested.

Krieg ‘371, Hutcherson or Agrawal in view of Krieg ‘371, and U.S. Patent No. 6,689,757 (Craig)

Claims 1, 11, 21, 23, 24 and 25 are rejected under 35 U.S.C. §103 as being unpatentable over Krieg (‘371), Hutcherson or Agrawal in view of Krieg (‘371) and Craig. According to the Examiner, Krieg ‘371 “teaches a cytokine as an adjuvant in combination with the CpG containing oligo” and Craig teaches co-administration of B7-1 co-stimulatory molecules with a nucleic acid and antigen. The Examiner concludes that “one of ordinary skill in the art would have been motivated to employ a B7 costimulatory molecule in combination with an antigen/oligo composition as taught by the combined references”. If the double recitation of Krieg ‘371 is an error, the Examiner is asked to clarify the rejection.

Claim 24 has been cancelled. Applicant traverses in part.

The Davis Declaration referred to above removes Krieg ‘371 as a prior art reference. The addition of Craig does not provide the deficiencies of the combination of earlier references. Rather the addition of Craig leads to an immunization scheme in which at least one epitope is

administered in the form of a nucleic acid which must be expressed in vivo. The pending claims explicitly *exclude* antigens encoded by a nucleic acid vector.

Accordingly, withdrawal of this rejection is respectfully requested.

U.S. Patent No. 6,042,838 (Briles) in view of Hutcherson or Agrawal

Claims 1, 3-9, 12-13, 15-20, 22, 26-28 and 125-132 are rejected under 35 U.S.C. §103(a) as being unpatentable over Briles in view of Hutcherson or Agrawal. The Examiner states that “it would have been obvious for an ordinary skilled artisan, to modify the immunogenic composition .. and the method for inducing mucosal immunity against pneumococcal colonization and systemic infection taught by Briles et al. by utilizing an immunostimulatory oligonucleotide having the CpG motif as taught by either Hutcherson or Agrawal in either a free form or in a non-covalently linkage with PSPA antigens as an adjuvant”.

Applicant traverses in part. Claim 1 excludes *S. pneumoniae* antigens. Briles teaches intranasal administration of whole *S. pneumoniae* and immunogenic fragments thereof. The immunization scheme of Briles may include but does not require an adjuvant. Briles does not teach that its immunization method extends beyond *S. pneumoniae* antigens nor does it teach adjuvants that are CpG oligonucleotides. The combination of Briles with Hutcherson or Agrawal does not result in the claimed invention. For example, the combination of Briles and Hutcherson does not result in the use of a CpG oligonucleotide as an adjuvant because neither reference recognizes a CpG motif as immunostimulatory. Additionally, with respect to claim 1, the combination results in immunization with an antigen excluded from the claim. With respect to claim 131, the combination does not teach that a CpG oligonucleotide is administered to a mucosal site different from the mucosal site exposed to antigen. With respect to claim 136, the combination does not teach the combined use of oligonucleotide and non-oligonucleotide adjuvants.

Accordingly, withdrawal of this rejection is respectfully requested.

Briles in view of Hutcherson and Agrawal, and in further view of Krieg '555

Claims 1, 3-9, 12-13, 15-20, 22, 26-28 and 125-132 are rejected under 35 U.S.C. §103(a) as being unpatentable over Briles in view of Hutcherson and Agrawal, and in further view of Krieg '555.

Krieg '555 does not add cure or add to the deficiency in the earlier combination of references. The combination of references with Krieg '555 still does not result in the all the limitations of claims 1, 131 and 136.

Accordingly, withdrawal of this rejection is respectfully requested.

Briles in view of Hutcherson and Agrawal, and in further view of Craig

Claims 1, 24 and 25 are rejected under 35 U.S.C. §103 as being unpatentable over Briles in view of Hutcherson and Agrawal, and in further view of Craig. Specifically, the Examiner asserts that "one of ordinary skill would have been motivated to employ a B7 costimulatory molecule in combination with an antigen/oligo combination as taught by the combined cited references".

Claim 24 has been cancelled. Applicant traverses in part. Craig does not cure the deficiency in the earlier combination of references. Craig requires that one epitope in its immunization scheme be encoded by a nucleic acid. The addition of Craig therefore results in an immunization strategy in which at least one antigen is encoded by a nucleic acid. Claim 1 explicitly excludes such antigens. The combination therefore does not render obvious claims 1 and 25.

Accordingly, withdrawal of this rejection is respectfully requested.

Serial No.: 09/316,199
Conf. No.: 7506

- 14 -

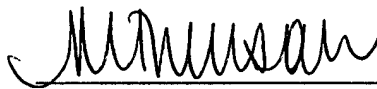
Art Unit: 1632

Conclusion

A favorable action is respectfully requested. **The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance and prior to the issuance of a further action.**

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,



Maria A. Trevisan, Reg. No. 48,207
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
Telephone: (617) 646-8000

Docket No.: C1040.70006US00
Date: May 2, 2005
x05/02/05x